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(71) Applicant *(for all designated States except US)*: **SANDOZ AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **FRANCO, Cristian, Ramiro** [AR/AR]; Santa Teresa Street No.176, Tortuguitas, Buenos Aires (AR). **KOFLER, Nikolaus** [AT/AT]; Feldweg 44, A-6134 Vomp (AT). **MENDIOROZ, Elsa, Elena** [AR/AR]; Eleodoro Lobos 212 Dto 18, 1405 Buenos Aires (AR). **DOMINGUEZ, Silvia, E., S.** [AR/AR]; Sandoz S.A., Cramer 4130, 1429 Buenos Aires (AR).

(74) Agent: **LIPHARDT, Bernd**; Novartis AG, Corporate Intellectual Property, CH-4002 Basel (CH).

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(54) Title: NEW COMPOSITIONS CONTAINING TAXANE DERIVATIVES

(57) Abstract: Novel taxane derivatives based compositions comprising a solution of such derivatives in a surfactant. These compositions can be used to prepare perfusion solutions.

New compositions containing Taxane derivatives

The present invention relates to new compositions suitable for intravenous injection or infusion and, especially pharmaceutical dosage forms comprising taxane derivatives, especially docetaxel or paclitaxel.

Taxane derivatives, such as docetaxel and paclitaxel are well known and established drugs in the treatment of malignant tumours. For example, docetaxel is marketed by Sanofi-Aventis under the trade name Taxotere® and paclitaxel is marketed by Bristol-Myers-Squibb under the trade name Taxol®. The low solubility of docetaxel and paclitaxel are well documented and is the major cause for preparation of the formulation for injection containing surfactant. EP 0 593 601, EP 0 593 656, EP 0 672 912 and EP 1 117 440 disclose the use of polysorbates, polyoxyethylene glycol esters and polyethoxylated castor oils as suitable surfactants.

The currently marketed formulation of docetaxel comprises a two compartment formulation composed of a vial containing a solution of docetaxel in polysorbate 80 and a solvent vial containing an aqueous solution of ethanol. This two compartment system makes the handling for the pharmacist complicated. The system requires two dilutions prior to administration to the patient. The drug vials has prior to use to be reconstituted with the solvent vial making sure that the polysorbate 80 is properly reconstituted but without significant foaming. This solution then has to be further diluted by injection of the appropriate amount of solution into an infusion bag. The currently marketed formulation contains an overfill for both the drug vial and the solvent vial. Thus apart from the handling this implies a risk for the proper dosing to the patient.

Moreover, the currently marketed formulation of Taxotere® is fairly complicated in manufacturing as it involves preparation of a solution of docetaxel in polysorbate 80 and ethanol with subsequent evaporation of ethanol and filling of the viscous solution. This process requires special equipment in term of evaporation, filtration and filling.

In contrast one compartment formulations contain a solution of the drug in a single vial with a well known concentration of the solution. This solution has to be withdrawn from the vial and injected into the infusion bag. As the vial does not have to be reconstituted and homogenized prior to use there is no risk of foaming.

Rhone-Poulenc Rorer did a series of investigations to replace Cremophor EL (polyethoxylated castor oil) by polysorbate 80 which is preferred with reference to anaphylactic reactions. Rhone-Poulenc Rorer additionally did investigations to minimize and/or eliminate the level of ethanol in the formulation. They additionally did investigations to minimize the level of polysorbate 80 in the formulation to finally achieve a ration of docetaxel to polysorbate 80 of 40 mg to 1 ml. Rhone-Poulenc Rorer finally concluded that proper chemical and physical characteristics of the formulation with minimum levels of polysorbate 80 and ethanol could only be achieved by formulating Taxotere® as a two compartment system composed of a vial containing a solution of docetaxel in polysorbate 80 and a solvent vial containing an aqueous solution of ethanol.

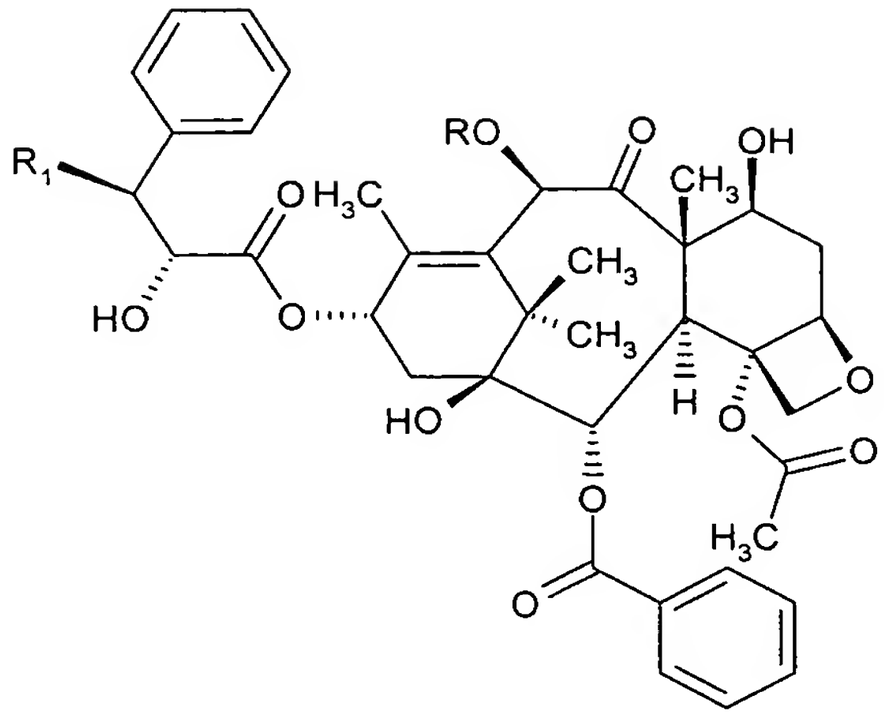
The marketing composition of docetaxel is complicated to manufacture and require special equipments. Moreover, said marketed formulations contain ethanol, therefore it is not possible to exclude the risk of alcoholism, especially when a patient is submitted to repetitive treatments.

It would be therefore desirable to develop alternative compositions having the same chemical and physically stability of the marketed taxane derivatives, the manufacturing process of said compositions being simplified, allowing the industrial preparation thereof and the production costs to be reduced.

The applicant has now surprisingly found alternative taxane derivatives containing compositions comprising glycofurol as a solvent or ethanol free compositions. The compositions according to the invention are easily manufactured and are chemically and physically stable.

The first object of the present invention is related to a pharmaceutical composition suitable for intravenous injection or infusion comprising:

- a taxane derivative of formula (I)



(I)

wherein R represents a hydrogen atom or an acetyl radical and R_1 represents a ter-butoxycarbonylamino or a benzoylamino radical, especially docetaxel and paclitaxel, more particularly docetaxel,

- glycofurol as a solvent and,
- a physiologically acceptable surfactant (i.e. a surface active agent) selected from the group consisting of cremophor, a polyethylene glycol ether or ester and a polyoxyethylene glycol ether or ester.

According to the present invention the term "chemical and physical stability" is understood to mean that the composition does not exhibit any visible precipitation after at minimum of 3 months when stored under accelerated stability conditions (40° C / 75 % relative humidity). In addition the composition does not show any significant degradation meaning that degradation products are formed at a level of less than 5 %, preferably less than 2 % when stored under accelerated stability conditions (40° C / 75 % relative humidity).

According to the present invention the phrase "pharmaceutical composition suitable for intravenous injection or infusion" is understood to mean that prior to be used the composition according to the present invention is diluted to the adequate medically recommended concentration for injection or infusion in 0.9 % saline, 5 % glucose or another pharmaceutically acceptable medium for injection or infusion, Accordingly, following the dilution to the adequate medically recommended concentration for injection or infusion in 0.9 % saline, 5 % glucose or another pharmaceutically acceptable medium for injection or infusion, the composition according to the present invention will be suitable for intravenous injection or infusion.

Cremophor is also known as polyoxyl 35 castor oil or polyethoxylated castor oil. A Preferred cremophor is selected from the group consisting of cremophor EL and cremophor ELP.

Preferred polyethylene glycol ether or ether is "Solutol", chemically known as polyethylene glycol-15-hydroxystearate and commercialized by BASF under the name Solutol® HS 15.

Preferred polyoxyethylene glycol ether or ester is a polysorbate marketed under the name "Tween", especially polysorbate 80, chemically known as polyoxyethylene sorbitan monooleate, (x)-sorbitan mono-9-octadecenoate poly(oxy-1,2-ethanediyl).

Preferably, the composition according to the first object of the invention further contains citric acid.

In a preferred embodiment the composition according to the first object of the invention is presented in the form of a one compartment system.

In a still preferred embodiment the composition according to the first object of the invention, the composition comprises the following ratio of components :

COMPONENT	RATIO OF COMPONENTS
Taxane of formula (I)	1 mg
Glycofurol	0.015 – 0,043 ml
Surfactant	12 - 35 mg

A particularly preferred composition according the first object of the invention is a composition corresponding to a one compartment system comprising a solution of docetaxel in a mixture of glycofurol, citric acid and a surfactant selected from the group consisting a polysorbate 80, Cremophor ELP or Solutol HS 15, especially polysorbate 80.

The compositions according to the invention are chemically and physically stable using the same ration of docetaxel versus polysorbate 80 as Sanofi-Aventis is doing for Taxotere®. This is essential to control side effects of the formulation and to maintain bioavailability of docetaxel. It is well documented that changes in surfactants impact bioavailability of sparingly water soluble pharmaceutical ingredients like docetaxel.

According to the present invention the phrase "chemical and physical stability" is understood to mean that the composition does not exhibit any visible precipitation after at minimum of 3 months when stored under accelerated stability conditions (40° C / 75 % relative humidity). In addition the composition does not show any significant degradation meaning that

degradation products are formed at a level of less than 5 %, preferably less than 2 % when stored under accelerated stability conditions (40° C / 75 % relative humidity).

The composition according to the first object of the invention is free of ethanol avoiding any risk of ethylism which is an additional advantage versus Taxotere®. In addition the formulation can be processed by a simple aseptic filling process with standard equipment not implying any special investment into manufacturing equipment.

The compositions according to first object of the invention corresponding to a one compartment system are especially applicable to routine hospital procedures in contrast to the one compartment system described in EP 0 563 601 and cited by reference in EP 0 671 912. The composition of the invention corresponding to a one compartment system are more convenient to handle by pharmacists and minimizing the risk of improper dosing by providing a solution with a well defined concentration for injection into the infusion bag.

According to the present invention the phrase "a composition in the form of a one compartment system" is defined as a pharmaceutical presentation for a parenteral product which contains the drug substance and a suitable solvent or solvent system within one vial, ampoule or an equivalent pharmaceutical presentation and does not require addition of any other solvents or solvent systems to the vial, ampoule or equivalent pharmaceutical presentation prior to withdrawal of the content from the pharmaceutical presentation.

Moreover, the applicant has surprisingly found additional taxane derivatives containing composition demonstrating proper characteristics in term of chemical and physical stability.

Accordingly, a second object of the present invention is related to a pharmaceutical composition suitable for intravenous injection or infusion comprising a taxane derivative of formula (I) as previously described, preferably docetaxel or paclitaxel, more preferably docetaxel; a physiologically acceptable solvent, preferably selected from the group consisting of glycofurol, DMSO, polyethylene glycol, glycerol, propanediol, polypropylene glycol, benzyl alcohol and N-methyl-2-pyrolidone; and polysorbate as surfactant, provided that said solvent is not ethanol and/or water and said composition is presented in form of a one compartment system.

In a still preferred embodiment the composition according to the second object of the invention, the composition comprises the following ratio of components :

COMPONENT	RATIO OF COMPONENTS
Taxane of formula (I)	1 mg
Solvent	0.019 – 0,040 ml
Polysorbate	20 – 32 mg

A third object of the present invention is related to pharmaceutical compositions suitable for intravenous injection or infusion comprising in a one compartment system a taxane derivative of formula I as described previously, especially docetaxel, a physiologically acceptable solvent and a physiologically acceptable surfactant, provided that said surfactant is not a polysorbate and said taxane derivative of formula I is not paclitaxel.

With the exception of polysorbates, any suitable surfactant (i.e. a surface active agent) can be used in the context of the third object of the present invention. The surfactant desirably is physiologically acceptable. Physiologically acceptable surfactants are generally known in the art and include various detergents and phospholipids. It is preferred that the physiologically acceptable surfactant is selected from the group consisting of cremophor, a polyethylene glycol ether or ether and a polyoxyethylene glycol ether or ester.

Preferred solvent is selected from the group consisting of glycofurol, ethanol, DMSO, polyethylene glycol, glycerol, propanediol, polypropylene glycol, benzyl alcohol and N-methyl-2-pyrolidone.

Preferred surfactant is selected in the group consisting of cremophor EL, cremophor ELP; a polyethylene glycol ether or ester, particularly solutol and polyoxyethylene glycol ether or ester, not being polysorbate, especially polyoxyethylene fatty acid esters such as Myrj™ commercialized by Uniqema.

In a preferred embodiment the composition according to the third object of the invention, the composition comprises the following ratio of components :

COMPONENT	RATIO OF COMPONENTS
Taxane of formula (I)	1 mg
Solvent	0.010 – 0,045 ml
Surfactant	12 - 35 mg

The composition according to the second or third object of the invention further contains citric acid.

Accordingly, a preferred embodiment according to the present invention is to a pharmaceutical composition suitable for intravenous injection or infusion comprising in a one compartment system a taxane derivative of formula (I) as previously described, particularly docetaxel, a physiologically acceptable solvent, citric acid and a physiologically acceptable surfactant, provided that said surfactant is not polysorbate and that said taxane derivative of formula (I) is not paclitaxel.

Preferably the solvent is selected from the group consisting of glycofurol, ethanol, DMSO, polyethylene glycol, glycerol, propanediol, polypropylene glycol, benzyl alcohol and N-methyl-2-pyrolidone.

Preferably the surfactant is selected in the group consisting of cremophor EL, cremophor ELP, and a polyethylene glycol ether or ester, particularly solutol or polyoxyethylene fatty acid esters.

The injectable compositions according to the invention are intended for the preparation of a solution for infusion. Said compositions will be mixed, in particular to provide a final concentration of between 0.3 and 0.74 mg per millilitre, with the perfusion fluid, which can be a 0.9 % saline or 5 % glucose solution.

The compositions according to the present invention are easily prepared using by well known process and techniques with standard equipment.

This invention will be better understood from the examples that follow. However, these examples illustrate but do not limit the invention. Those skilled in the art will readily appreciate that the specific process and results discussed are merely illustrative of the invention as described more fully in the claims that follow thereafter.

The following non-limiting examples illustrate further aspects of the invention.

Vials with one compartment containing 20mg or 80mg of docetaxel.

Example 1

CONCENTRATION	Vial 20 mg	Vial 80 mg
Docetaxel	20 mg	80 mg
Citric Acid	2 mg	8 mg
Glycofurol	Ad 1 ml (449 mg)	Ad 4 ml (1.796 mg)

Solutol	600 mg	2.400 mg

Citric acid (180 mg) is dissolved in approximately 30 ml of glycofurol with stirring at ambient temperature. Docetaxel (1.8 g) is added under stirring until complete dissolution. Solutol (54.0 g) is added to the solution under stirring to get a homogenous solution. Fill up to 90 ml with glycofurol and mix. The solution is filtered and filled into vials. The vials are closed with fluoropolymer coated rubber stoppers and sealed with crimp caps.

Example 2

CONCENTRATION	Vial 20 mg	Vial 80 mg
Docetaxel	20 mg	80 mg
Citric Acid	2 mg	8 mg
Ethanol Absolute	Ad 1 ml (331 mg)	Ad 4 ml (1.324 mg)
Solutol	600 mg	2.400 mg

Citric acid (180 mg) is dissolved in approximately 30 ml of ethanol absolute with stirring at ambient temperature. Docetaxel (1.8 g) is added under stirring until complete dissolution. Solutol (54.0 g) is added to the solution under stirring to get a homogenous solution. Fill up to 90 ml with ethanol absolute and mix. The solution is filtered and filled into vials. The vials are closed with fluoropolymer coated rubber stoppers and sealed with crimp caps.

Example 3

CONCENTRATION	Vial 20 mg	Vial 80 mg
Docetaxel	20 mg	80 mg
Citric Acid	2 mg	8 mg
Glycofurol	Ad 1 ml (715 mg)	Ad 4 ml (2.862 mg)
Cremophor ELP	351 mg	1.405 mg

Citric acid (180 mg) is dissolved in approximately 30 ml of glycofurol with stirring at ambient temperature. Docetaxel (1.8 g) is added under stirring until complete dissolution. Cremophor ELP (31.59 g) is added to the solution under stirring to get a homogenous solution. Fill up to 90 ml with glycofurol and mix. The solution is filtered and filled into vials. The vials are closed with fluoropolymer coated rubber stoppers and sealed with crimp caps.

Example 4

CONCENTRATION	Vial 20 mg	Vial 80 mg
Docetaxel	20 mg	80 mg
Cirtic Acid	2 mg	8 mg
Ethanol Absolute	Ad 1 ml (527 mg)	Ad 4 ml (2.107 mg)
Cremophor ELP	351 mg	1.405 mg

Citric acid (180 mg) is dissolved in approximately 30 ml of ethanol absolute with stirring at ambient temperature. Docetaxel (1.8 g) is added under stirring until complete dissolution. Cremophor ELP (31.59 g) is added to the solution under stirring to get a homogenous solution. Fill up to 90 ml with glycofurol and mix. The solution is filtered and filled into vials. The vials are closed with fluoropolymer coated rubber stoppers and sealed with crimp caps.

Example 5

CONCENTRATION	Vial 20 mg	Vial 80 mg
Docetaxel	20 mg	80 mg
Citric Acid	2 mg	8 mg
Glycofurol	Ad 1 ml (553 mg)	Ad 4 ml (2.213 mg)
Polysorbate 80	520 mg	2.080 mg

Citric acid (180 mg) is dissolved in approximately 30 ml of glycofurol with stirring at ambient temperature. Docetaxel (1.8 g) is added under stirring until complete dissolution. Polysorbate 80 (46.8 g) is added to the solution under stirring to get a homogenous solution. Fill up to 90 ml with glycofurol and mix. The solution is filtered and filled into vials. The vials are closed with fluoropolymer coated rubber stoppers and sealed with crimp caps.

Example 6

CONCENTRATION	Vial 20 mg	Vial 80 mg
Docetaxel	20 mg	80 mg
Citric Acid	2 mg	8 mg
Ethanol absolute	Ad 1 ml (630 mg)	Ad 4 ml (2.520 mg)
Polysorbate 80	520 mg	2.080 mg

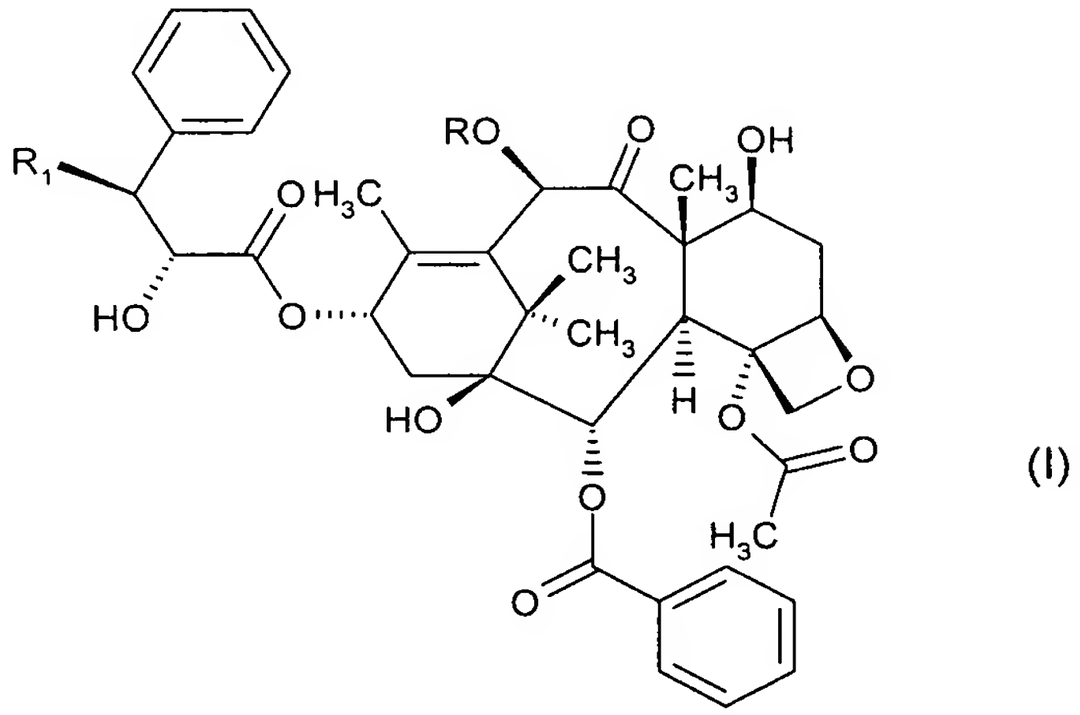
Citric acid (180 mg) is dissolved in approximately 30 ml of ethanol absolute with stirring at ambient temperature. Docetaxel (1.8 g) is added under stirring until complete dissolution.

Polysorbate 80 (46.8 g) is added to the solution under stirring to get a homogenous solution. Fill up to 90 ml with glycofurol and mix. The solution is filtered and filled into vials. The vials are closed with fluoropolymer coated rubber stoppers and sealed with crimp caps.

Claims

1. Pharmaceutical composition suitable for intravenous injection or infusion comprising :

- a taxane derivative of formula (I)



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wherein R represents a hydrogen atom or an acetyl radical and R_1 represents a ter-butoxycarbonylamino or a benzoylamino radical,

- glycofurol as a solvent and,
- a physiologically acceptable surfactant selected from the group consisting of cremophor, a polyethylene glycol ether or ester and a polyoxyethylene glycol ether or ester.

2. Pharmaceutical composition according to claim 1, wherein said cremophor is selected from the group consisting of cremophor EL and cremophor ELP.

3. Pharmaceutical composition according to claim 1, wherein said polyethylene glycol ether or ester is solutol.

4. Pharmaceutical composition according to claim 3, wherein said polyoxyethylene glycol ether or ester is polysorbate.

5. Pharmaceutical composition according to any of the previous claims, wherein said taxane derivative of formula I is selected from the group consisting of docetaxel and paclitaxel.

6. Pharmaceutical composition according to any of the previous claims, wherein the composition is presented in the form of a one compartment system.

7. Pharmaceutical composition suitable for intravenous injection or comprising a taxane derivative of formula I as defined in claim 1, a physiologically acceptable solvent and polysorbate as surfactant, provided that said solvent is not ethanol and/or water, said composition is presented in the form of a one compartment system.

8. Pharmaceutical composition according to claim 7, wherein said taxane derivative of formula I is selected from the group consisting of docetaxel and paclitaxel.

9. Pharmaceutical composition suitable for intravenous injection or infusion comprising in a one compartment system a taxane derivative of formula (I) as defined in claim 1, a physiologically acceptable solvent and a physiologically acceptable surfactant, provided that said surfactant is not a polysorbate and that said taxane derivative of formula (I) is not paclitaxel.

10. Pharmaceutical composition according to claim 9, wherein said solvent is selected from the group consisting of glycofurol, ethanol, DMSO, polyethylene glycol, glycerol, propanediol, polypropylene glycol, benzyl alcohol and N-methyl-2-pyrolidone.

11. Pharmaceutical composition according to claim 10, wherein said surfactant is selected in the group consisting of cremophor EL or cremophor ELP.

12. Pharmaceutical composition according to claims 9 and 10, wherein said surfactant is a polyethylene glycol ether or ester, particularly solutol.

13. Pharmaceutical composition according to claims 9 and 10 wherein said wherein said surfactant is a polyoxyethylene glycol ether or ester not being polysorbate, particularly polyoxyethylene fatty acid esters.

14. Pharmaceutical composition according to one of claims 9 to 13, wherein said taxane derivative of formula I is docetaxel.

15. Pharmaceutical composition according to one of claims 1 to 15 containing citric acid.